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EXAMINER

KERR, KATHLEEN M

ART UNIT PAPER NUMBER

1652

DATE MAILED: 10/21/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/851,650

Applicant(s)

BARR ET AL.

Examiner

Kathleen M Kerr

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 July 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 5, 6, 8-14, 16, 30-34, 37 and 39-41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5, 6, 8-14, 30-34, 37 and 39-41 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other: _____

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-final rejection (Paper No. 11, mailed on January 28, 2003), Applicants filed an amendment and response received on July 28, 2003 (Paper No. 12). Said amendment amended Claims 1, 3, 8, 10, 11-14, 16, 30, 32, 37, and 39, cancelled Claims 4, 35, 36, and 38, and added new Claims 40-41. Thus, Claims 1-3, 5, 6, 8-14, 16, 30-34, 37, and 39-41 are pending in the instant Office action and will be examined herein.

Priority

2. As previously noted, the instant application is granted the benefit of priority for provisional application 60/033,193 filed on December 18, 1996, non-provisional applications 08/989,332 filed in December 11, 1997 and 09/422,073 filed on October 21, 1999, and the international application PCT/US97/23014 filed on December 12, 1997. The priority date granted for purposes of prior art is December 18, 1996.

Drawings

3. As previously noted, the drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Withdrawn - Objections to the Specification

4. Previous objection to the specification is objected to for not updating patent application number references throughout the specification is withdrawn by virtue of Applicant's amendment.
5. Previous objection to the specification for confusing points "gris" and "lac^{lq} [?]" is withdrawn by virtue of Applicants' amendment.
6. Previous objection to the specification for typographical errors is withdrawn by virtue of Applicants' amendment.

Maintained - Objections to the Specification

7. Previous objection to the specification for lacking complete continuity data in the first paragraph is maintained. Applicants have amended the first paragraph but omitted reference to international application PCT/US97/23014 filed on December 12, 1997. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

Withdrawn - Objections to the Claims

8. Previous objection to Claim 3 for lacking specific antecedent basis is withdrawn by virtue of Applicants' amendment.
9. Previous objection to Claim 11 for lacking consistency is withdrawn by virtue of Applicant's amendment.

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Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

10. Previous rejection of Claim 1 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviation “ACP” is withdrawn by virtue of Applicant’s amendment.
11. Previous rejection of Claim 4 under 35 U.S.C. § 112, second paragraph, is withdrawn by virtue of Applicant’s cancellation of said claim.
12. Previous rejection of Claims 8-16 under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of “said first vector” and “said second vector” is withdrawn by virtue of Applicants’ amendment.
13. Previous rejection of Claims 13-14 under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of “said first and second module” is withdrawn by virtue of Applicants’ amendment.

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14. Previous rejection of Claims 13 and 14 under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “different” is withdrawn by virtue of the Examiner’s reconsideration. It is noted, however, that even a single nucleotide change between the first and second PKS genes makes these genes “different” since no other definition is found in the claims.

15. Previous rejection of Claim 14 under 35 U.S.C. § 112, second paragraph, as being indefinite for the antecedent basis of “said nucleotide sequence encoding at least one module” is withdrawn by virtue of Applicants’ amendment.

16. Previous rejection of Claim 14 under 35 U.S.C. § 112, second paragraph, as being indefinite for the abbreviations “KR”, “DH” and “ER” is withdrawn by virtue of Applicant’s amendment.

New or Maintained – 35 U.S.C. § 112, second paragraph

17. Previous rejection of Claim 10 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “expression system for a cell-based detection system for a functional polyketide” is maintained. Applicants’ arguments have been fully considered but are not deemed persuasive. Applicants argue that the term is defined by the specification, particularly in light of Broach & Thorner. The Examiner disagrees. Broach & Thorner teach generic high-throughput screening techniques, none of which are specific to polyketide synthases. Neither the specification nor the art define a “functional polyketide”; what “function” is required? Clarification of the metes and bounds of this phrase is required.

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18. Previous rejection of Claims 30-34, 37, 39, and 40-41(new) under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “functional polyketide synthase catalytic activity” is maintained. Applicants’ arguments have been fully considered but are not deemed persuasive. Firstly, the concept of “a coding region of ... a catalytic activity of a polyketide synthase” is unclear. In this context, the activity is a tangible product when, in reality, the activity does not have a “coding region. Secondly, as previously noted, PKSs are multifunctional proteins. This claim, then, reads on any yeast vector encoding a protein with an activity found in PKSs, i.e., any acyltransferase, any enoyl reductase, etc. Moreover, the protein need not be a PKS protein, but merely have the activity like one. The claims imply a PKS gene must be in vector, but, if read with the broadest reasonable interpretation and without any limitation on the source of the gene in the vector, the scope is enormous. With scope so broad, clarity is required.

19. (New) Claims 1-3, 5, 6, 10, 12-14, and 40-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 1, 10, and 12, the phrase “encodes for” followed by a protein or other molecule is improper since nucleotide sequences either --- encode--- or ---code for---. Correction is required.

20. (New) Claims 32, 34, 37, and 39-41 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 32 and 37, the requirement of the holo ACP synthase being effective in the pantetheinylation of the PKS is unclear since the

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limitations in Claim 30 do not require a PKS enzyme, but merely its activity, as noted above in another rejection under 35 U.S.C. § 112, second paragraph.

21. (New) Claim 41 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The inclusion of “ACPS” as a holo ACP synthase “effective in the pantetheinylation of said PKS” is confusing since the specification describes ACPS from *E. coli* as lacking this functionality (see Example 6). Clarification for its inclusion is required.

Withdrawn – 35 U.S.C. § 112, first paragraph

22. Previous rejection of Claim 4 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn by virtue of Applicants cancellation of said claim.

23. Previous rejection of Claims 1-6, 16, 32, 34, 37, and 39 under 35 U.S.C. § 112, first paragraph, scope of enablement, is withdrawn in part. Inclusion of the phrase “holo ACP synthase ...effective in the pantetheinylation of said PKS” overcomes the scope of enablement related to using these systems to express type I and fungal PKSs.

New or Maintained – 35 U.S.C. § 112, first paragraph

24. Previous rejection of Claims 1-3, 5, 6, 16, 32, 34, 37, 39, and 40(new) under 35 U.S.C. § 112, first paragraph, written description, is maintained. Applicant’s arguments have been fully considered but are not deemed persuasive for the following reasons. Applicants argue that a precise definition of holo ACP synthases is provided in the specification on page 7, for example.

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The Examiner disagrees because what is required to adequately describe the claimed genus is genes encoding holo ACP synthases that are “effective in the pantetheinylation of said PKS”. In the examples of the instant specification, entD, GsP, and sfp holo ACP synthases are effective, but ACPS holo ACP synthase is not. Thus, it is impossible for one of skill in the art to be able to predict which holo ACP synthases are “effective in the pantetheinylation of said PKS” and which are not by virtue of the instant disclosure in combination with the art. What must have adequate written description is the subset of holo ACP synthases that are effective. From the instant specification, the characteristics of this subset are unclear so that one could predict the other members of this subset.

Applicants also argue that the art in this field is “mature” by virtue of Lambalot *et al.*; however, Lambalot *et al.* fail to adequately describe the claimed subgenus, that is pantetheinylation-effective holo ACP synthases, so that one of skill in the art would be able to predict which holo ACP synthases are effective and which are not.

With respect to the inclusion of new Claim 40, the limitation of being from *Bacillus*, while limiting the genus from which “effective” holo ACP synthases can be drawn, does not predictably define which holo ACP synthases are effective ones. Thus, the same inadequacies of written description are clear.

25. Previous rejection of Claims 1, 2, 5, 6, and new Claims 16, 32, 34, 37, and 39-41 under 35 U.S.C. § 112, first paragraph, scope of enablement, is maintained in part as related to modified host cells that use type II PKSs wherein the holo ACP synthase is effective in pantetheinylation of said type II PKS. Applicants’ arguments have been fully considered but are not deemed persuasive. Applicants argue “general features of aromatic, modular, and fungal

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PKS systems are shown” in the specification and hybrid type II systems are incorporated by reference. While the Examiner does not disagree, these discussions do not enable producing host cells that produce polyketides by virtue of expression systems for a holo ACP synthase and a type II PKS. Applicants argue that Example 11 describes type II PKSs for the claimed methods; however, Example 11 includes no required use of a holo ACP synthase (see page 27, line 14 saying “if necessary”). Additionally, this Example describes a postulated experiment and not a performed experiment since the product is “predicted to be” the structure on page 27. It is wholly unpredictable if holo ACP synthases provide the same pantetheinylation function for type II PKS systems as they do for fungal and type I systems.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

26. Previous rejection of Claims 30-31 and 33 under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,712,146) is withdrawn by virtue of Applicant’s arguments. As pointed out by Applicants, *S. coelicolor* is a bacterium, not a yeast; thus, the teachings of ‘146 alone cannot anticipate the instant claims.

27. Previous rejection of Claims 30-31 and 33 under 35 U.S.C. § 102(b) as being anticipated by Shen *et al.* (1993) is withdrawn by virtue of Applicant’s arguments. As pointed out by Applicants, *S. coelicolor* is a bacterium, not a yeast; thus, the teachings of Shen *et al.* (1993) alone cannot anticipate the instant claims.

28. Previous rejection of Claims 35-36 and 38 under 35 U.S.C. § 102(b) as being anticipated by Gramajo *et al.* is withdrawn by virtue of Applicants’ cancellation of said claims.

29. Previous rejection of Claims 35-36 and 38 under 35 U.S.C. § 102(b) as being anticipated by Roberts *et al.* is withdrawn by virtue of Applicants' cancellation of said claims.

Maintained - Claim Rejections - 35 U.S.C. § 102

30. Previous rejection of Claims 8, 9, 11, and 12 under 35 U.S.C. § 102(e) as being anticipated by Khosla *et al.* (USPN 5,712,146) is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that Khosla *et al.* do not teach a host cell "which in unmodified form does not produce polyketides" in the form of *S. coelicolor* CH999; this is not the case. While it is true that *S. coelicolor* in general produce polyketides, CH999 do not produce polyketides and can be considered "unmodified" since the claims do not require the host cells to be naturally-occurring.

Maintained - Claim Rejections - 35 U.S.C. § 103

31. Previous rejection of Claims 1-2 and 5 under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (1995) in view of Shen *et al.* (1993) is maintained. Applicants' arguments have been fully considered but are not deemed persuasive. Applicants argue that no motivation to combine the teachings of Lambalot and Shen is found in the art; the Examiner disagrees. As previously noted, "It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a host cell containing ACPS and the *tcmJKLMN* genes for heterologous production, particularly on separate vectors since both vectors are found separately in each reference, of tetracenomycin in *E. coli* because Lambalot *et al.* (1995) indicate that such combinations will "greatly facilitate mechanistic studies of acyl activating enzymes in ...

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polyketide ... biosynthesis” (see page 24661, last paragraph).” Applicants also argue that no reasonable expectation of success is found in the prior art. Again, the Examiner disagrees since Lambalot specifically suggests the combination and pantetheinylation occurs *in vitro*.

32. Previous rejection of Claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (1995) in view of Shen *et al.* (1993) and in view of Bierman *et al.* is maintained for the reasons noted above for the maintenance of the rejection of Claims 1, 2, and 5 over Lambalot and Shen.

33. Previous rejection of Claims 8, 9, 11, and 12 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Bierman *et al.* is maintained. Applicants’ arguments have been fully considered but are not deemed persuasive. Applicants argue that Khosla *et al.* do not teach a host cell “which in unmodified form does not produce polyketides” in the form of *S. coelicolor* CH999; this is not the case. While it is true that *S. coelicolor* in general produce polyketides, CH999 do not produce polyketides and can be considered “unmodified” since the claims do not require the host cells to be naturally-occurring.

34. Previous rejection of Claims 13 and 14 under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Oliynyk *et al.* is maintained. Applicants’ arguments have been fully considered but are not deemed persuasive. Applicants argue that Khosla *et al.* do not teach a host cell “which in unmodified form does not produce polyketides” in the form of *S. coelicolor* CH999; this is not the case. While it is true that *S. coelicolor* in

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general produce polyketides, CH999 do not produce polyketides and can be considered “unmodified” since the claims do not require the host cells to be naturally-occurring.

Maintained - Double Patenting

35. Previous rejection of Claims 1-3, 8, 9, 12-14, 16, 30-34, 37, and 39 under the judicially created doctrine of nonstatutory, obviousness-type double patenting with respect to USPN 6,033,883 is maintained. Applicants argue that this rejection is moot by virtue of a terminal disclaimer filed; no such filing has been received.

36. Previous rejection of Claims 1-3, 5, 6, 16, 32, 34, and 37 under the judicially created doctrine of nonstatutory, obviousness-type double patenting as being unpatentable over claims 1-5, 13, 8, 9, 11, and 12, respectively of U.S. Patent No. 6,258,566 is maintained. Applicants have presented no arguments thereto.

Summary of Pending Issues

37. The following is a summary of the issues pending in the instant application:

- a) The specification stands objected to for lacking complete continuity data in the first paragraph.
- b) Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “expression system for a cell-based detection system for a functional polyketide”.
- c) Claims 30-34, 37, 39, and 40-41(new) stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the term “functional polyketide synthase catalytic activity”.
- d) Claims 1-3, 5, 6, 10, 12-14, and 40-41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase “encodes for”.
- e) Claims 32, 34, 37, and 39-41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the requirement of the holo ACP synthase being effective in the pantetheinylation of the PKS is unclear since the limitations in Claim 30 do not require a PKS enzyme.

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- f) Claim 41 stands rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the inclusion of "ACPS" as a holo ACP synthase "effective in the pantetheinylation of said PKS" is confusing since the specification describes ACPS from *E. coli* as lacking this functionality.
- g) Claims 1-3, 5, 6, 16, 32, 34, 37, 39, and 40(new) stand rejected under 35 U.S.C. § 112, first paragraph, written description.
- h) Claims 1, 2, 5, 6, and new Claims 16, 32, 34, 37, and 39-41 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, as related to modified host cells that use type II PKSs wherein the holo ACP synthase is effective in pantetheinylation of said type II PKS.
- i) Claims 8, 9, 11, and 12 under 35 U.S.C. § 102(e) stand rejected as being anticipated by Khosla *et al.* (USPN 5,712,146).
- j) Claims 1-2 and 5 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (1995) in view of Shen *et al.* (1993).
- k) Claim 6 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Lambalot *et al.* (1995) in view of Shen *et al.* (1993) and in view of Bierman *et al.*
- l) Claims 8, 9, 11, and 12 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Bierman *et al.*
- m) Claims 13 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Khosla *et al.* (USPN 5,712,146) in view of Oliynyk *et al.*
- n) Claims 1-3, 8, 9, 12-14, 16, 30-34, 37, and 39 stand rejected under the judicially created doctrine of nonstatutory, obviousness-type double patenting with respect to USPN 6,033,883.
- o) Claims 1-3, 5, 6, 16, 32, 34, and 37 stand rejected under the judicially created doctrine of nonstatutory, obviousness-type double patenting as being unpatentable over claims 1-5, 13, 8, 9, 11, and 12, respectively of U.S. Patent No. 6,258,566.

Conclusion

38. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read 'Ach', with a long horizontal line extending to the right.

PONNATHAPUACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

KMK
October 14, 2003